Remarks/Arguments

Reconsideration of the above-identified application in view of the present amendment is respectfully requested.

By the present amendment, claims 25, 33, and 40 have been amended to recite that a therapeutically effective amount of an antibody that binds to factor B is administered to the subject, the therapeutically effective amount of the antibody does not decrease factor B levels in the blood, and the anti-factor B antibody in an *in vitro* assay has a greater effectiveness at preventing factor B binding to properdin-bound C3b than factor B binding to free C3b. Support for the limitation of administering a "therapeutically effective amount" of anti-factor B antibody can be found page 10, lines 15-26 of the specification. Support for the limitations that the anti-factor B antibody in an *in vitro* assay has a greater effectiveness at preventing factor B binding to properdin-bound C3b than factor B binding to free C3b can be found in Example 1 and Figure 2, which shows factor B binding to properdin bound C3b is inhibited by the factor B monoclonal antibodies in a dose dependent fashion at an IC50 of 5 nM, and Example 2, Figure 4, which shows factor B binding to free C3b is inhibited by the factor B monoclonal antibodies in a dose dependent fashion at an IC50 greater than 5 nM.

1. 35 USC 112 rejection of claims 25-37 and 39-44

Claims 25-37 and 39-45 stand rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The Office Action argues the Claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention.

The Office Action maintains the rejection from October 6, 2008 rejection that the limitation added to claims 25, 33, and 40, which recites "wherein administration of the antibody does not decrease factor B levels in the blood" is new matter because the cited examples are all *in vitro* assays, which do not include all the elements for the removal of immune complexes found in an *in vivo* environment, as is claimed, and there is no indication in any of the assays that reduction of factor B as a result of addition of anti-factor B antibody was measured, considered, or even pertinent to the assay.

The Office Action notes that Applicant's previous rebuttal to this argument is not convincing because it is noted that the earlier recitation of "preventing the formation of Bb" is in an *in vitro* assay as recited in the claims. However, "decrease factor B levels in the blood" reads on *in vivo*. Therefore, *in vitro* prevention of formation of Bb would not have inherently prevented the decrease of factor B level *in vivo*.

Applicant respectfully requests reconsideration of the 35 USC 112, first paragraph rejection of claims 25, 33, and 40 because one skilled in the art upon reading the application would so recognize that administration of the anti-factor B antibody does not decrease factor B levels in the blood and that this is an inherent function or property of the anti-factor B antibody.

As discussed in Applicant's response dated December 17, 2008, the limitation "wherein administration of the antibody does not decrease factor B levels in the

blood" is inherent based on the recitation in the claims and the specification that anti-factor B antibody prevents formation of Bb. Applicant states in this response that

> "during complement activation, the formation of Bb is intimately related to the factor B levels in the blood. In order for Bb to be generated in the blood, factor B must first complex C3b to form a C3bB complex. The factor B of the C3bB complex is then cleaved by factor D to form Bb and Ba. Thus, factor Bb is formed from factor B, and upon compliment activation, factor B levels in the blood cannot decrease unless factor B is cleaved to form factor Bb. Therefore, an anti-factor B antibody that prevents the formation Bb would implicitly and inherently not decrease factor B levels in the blood."

The concept that factor Bb is formed from factor B is illustrated on page 14, Fig. 8 of The Complement Facts Book, Morley et al., Academic Press (2000) (a copy of page 14, which is attached).

The specification and claims of the application provide support for the limitation that the anti-factor B antibody prevents formation of Bb. Page 4, line 13 and page 7, line 12 of the specification state, respectively, that the inhibitor molecule prevents the cleavage of factor B into Bb and inhibits the release of Bb. Neither of these recitations state preventing formation of Bb is limited to *in vitro* or *in vivo* applications. Although, the claims do recite that the anti-factor B antibody prevents formation of factor Bb in an *in vitro* assay, Applicant fails to see how this limits the understanding of the inherent properties or function of the anti-factor B antibody to *in vitro* applications.

The specification of the present application states at page 8 and page 9 that:

> "It would be evident to the one skilled in the art that in vitro studies of complement are representative of and predictive of the in vivo state of the complement system. By way of example, the use of in vitro ELISA (enzyme-linked immunosorbent assay) procedures to detect factor B associated with lipopolysaccharide (LPS) is a "simple, rapid and reliable method for the assessment of complement

> function particularly the detection of complement deficiency states" [19]. Thus, the in vitro technique can be used in vivo with the same likelihood of success in detecting alternative complement pathway activation in disease states. Furthermore, the standard rabbit erythrocyte hemolysis assay (described in Example 4), which assay is used to measure alternative complement pathway activity, is accepted in the art as being the "most convenient assay for the activity of the human alternative pathway" [20]."

One of ordinary skill in the art would recognize that *in vitro* studies are representative and predictive of the *in vivo* state of the complement system. In vitro techniques can be used *in vivo* with the same likelihood of success in detecting alternative complement pathway activation in disease states. Applicant bases this conclusion on two separate studies, cited above with Arabic numerals and located in the specification of the present invention. Accordingly, the fact that the claims recite the prevention of the formation of factor Bb is an *in vitro* assay does not limit this characteristic to an *in vivo* setting because the anti-facto B antibody would inherently function the same in both *in vitro* models and *in vivo* setting.

Moreover, Example 5 of the present application describes a cardiopulmonary tubing loop assay in which the anti-factor B antibody was administered to whole blood of a healthy donor. As discussed in Example 5, administration of anti-factor B antibody to the whole blood was found to inhibit formation of soluble membrane attack complex (MAC). As illustrated in the attached Fig. 8 of The Complement Facts Book, the formation of MAC is related to the factor B levels in the blood. In order for MAC to be generated in the blood, factor B must first complex C3b to form a C3bB complex. The factor B of the C3bB complex is then cleaved by factor D to form Bb and Ba. C3bBb or C3 convertase cleaves C3 and forms $(C3b)_2Bb$ or C5

convertase. C5 converstase cleaves C5 and complexes with C6, C7, C8, and C9 in the terminal pathway to form MAC. Therefore, an anti-factor B antibody that prevents the formation of MAC in human would implicitly and inherently not decrease factor B levels in the blood because cleavage of factor B is required for downstream MAC formation. Therefore, *ex vivo* prevention of formation of MAC in a whole blood cardiopulmonary bypass loop model would have inherently prevented the decrease of factor B level in vivo, since ex vivo techniques can be used with the same likelihood of success as in vivo techniques. One having ordinary skill in the art would recognize that an *in vitro* or *ex vivo* blood assay that prevents the formation of Bb would be representative and predictive of an assay that does not decrease factor B levels in the blood *in vivo*.

The Office Action further notes that an antibody that binds factor B can form immune complex with factor B and precipitate factor B out from blood circulation, which results in a decrease in the levels of factor B in the blood and thus prevent factor B being cleaved to form Bb and Ba. Therefore, preventing Bb formation does not inherently keep the level of factor B in the blood from decreasing.

In order to form a precipitable immune complex, there however needs to be a sufficiently high concentration of the antibody in the blood. Claims 25, 33, and 40 however have been amended to recite that the amount anti-factor B antibody administered to a subject is a therapeutically effective amount. A "therapeutically effective amount" of the antibody is defined in the specification as a sufficient amount of the antibody to treat disorders, at a reasonable benefit/risk ratio applicable to any medical treatment. One skilled in the art would recognize that an

amount of antibody administered to subject that is sufficient to precipitate factor B, which is a soluble protein, from the blood would not be a therapeutically effective amount as such a high concentration of antibody would cause reasonable risk in the subject. Accordingly, a therapeutically effective amount of anti-factor B antibody in contrast to the Examiner's assertion would not form a precipitable complex and result in a decrease of factor B in the blood.

Accordingly, claims 25, 33, and 40 do not contain new matter and withdrawal of the rejection of claims 25-37 and 39-44 is respectfully requested because one skilled in the art upon reading the application would so recognize that administration of the anti-factor B antibody does not decrease factor B levels in the blood and that this is an inherent function or property of the anti-factor B antibody.

2. 35 USC 103(a) rejection of claims 25-37 and 39-44

Claims 25-37 and 39-45 are rejected under 35 USC 103(a) as being obvious over Gupta-Bansal et al. (U.S. Patent 6,333,034 B1) in view of Owens et al. (*Journal of Immunological Methods,* 1994, 168:149-165).

The Office Action argues Gupta-Bansal et al. taught a method of inhibiting alternative complement pathway activation in blood of a subject in need thereof comprising administering an anti-factor P antibody and that it would be obvious to one of ordinary skill in the art to make an equivalent substitution of the anti-factor P antibody for an anti-factor B antibody because Gupta-Bansal et al. taught factor B and factor P are potential targets for therapeutic agents to inhibit the alternative pathway. The Office Action further notes one of ordinary skill in the art would have

been motivated to use an anti-factor B antibody that blocked binding of factor B to C3b to effectively block alternative pathway for therapeutic purposes.

As discussed above, 25, 33, and 40 have been amended to recite the anti-factor B antibody in an *in vitro* assay has a greater effectiveness at preventing factor B binding to properdin-bound C3b than preventing factor B binding to free C3b. Claims 25-37 and 39-44 are not obvious in view of Gupta-Bansal et al. and Owens et al. because Gupta-Bansal et al. in view of Owens et al. do not teach an anti-factor B antibody that in an *in vitro* assay has a greater effectiveness at preventing factor B binding to properdin-bound C3b than preventing factor B binding to free C3b.

As discussed above Gupta-Bansal et al. teach a method of inhibiting alternative complement pathway activation in blood of a subject in need thereof comprising administering an anti-factor P antibody. Gupta-Bansal et al. state that, in addition to factor P, factor B is a potential target for the development of therapeutic agents to inhibit the alternative pathway (col. 6, ll. 46-49). Gupta-Bansal et al. however neither teach nor suggest developing an anti-factor B antibody that in an *in vitro* assay has a greater effectiveness at preventing factor B binding to properdin-bound C3b than preventing factor B binding to free C3b. In fact, there is nothing to suggest identifying and/or selecting an anti-factor B antibody by this criteria.

Moreover, it would not be predictable nor would one have a reasonable expectation of success of developing an anti-factor B antibody that has a greater effectiveness at preventing factor B binding to properdin-bound C3b than preventing factor B binding to free C3b.

Gupta-Bansal et al. state at column 6, lines 54+:

> "However, similar to the experience with factor D, it has proven difficult to identify inhibitors of factor Bb proteinase activity that do not also inhibit serine proteinases involved in blood coagulation hemostasis (Whitty, A., 1996, IBC's Second Annual Conference on Controlling the Complement System for Novel Drug Development, Conference Binder). *In any case, we believe factor B is probably not the best target for the development of therapeutic agents to inhibit the alternative pathway. Factor B is an abundant serum protein* (.about.210 .mu.g/ml) (Clardy, C. W., 1994, Infect. Immun. 62:4539-4555; Liszewski, M. K. and J. P. Atkinson, 1993, In Fundamental Immunology, Third Edition. Edited by W. E. Paul. Raven Press, Ltd. New York) *and it would probably require a correspondingly high concentration of an inhibitor of factor B to effectively block activation of the alternative pathway.*"

(emphasis added)(col. 6, ll. 54- col. 7, ll. 2). Gupta-Bansal et al. explicitly states that Factor B is probably not the best target for the development of therapeutic agents to inhibit the alternative pathway because one would require a high concentration of an inhibitor of factor B, as opposed to factor P. In addition, Gupta-Bansal et al. further states that:

> "Monoclonal antibodies to human factor B, however, have been prepared and tested for their *in vitro* ability to block alternative complement pathway activation by endotoxin (LPS) (Clardy, C. W. 1994, Infect Immun. 62:4539-4555). *One of the four monoclonal anti-factor B antibodies tested was able to effectively block alternative pathway activation. The other three antibodies tested failed to block despite having affinities that were similar to the blocking antibody.* In three other studies of anti-factor B monoclonal antibodies that were cited by Clardy, et al., supra (1994), two monoclonals increased factor B activity by stabilizing the alternative pathway convertase, one increased factor B activity by enhancing binding of B to C3b, three decreased factor B activity by destabilizing the convertase and two decreased factor B activity by blocking binding of factor B to C3b." (col. 7, ll. 2-16).

These studies, cited by Gupta-Bansal et al., show the unpredictability of focusing on inhibiting the binding of factor B to C3b to inhibit activation of the alternative pathway. In one study, for example, only one of four anti-factor B

antibodies was able to block alternative pathway activation, while the other three antibodies failed to do so despite having affinities that were similar to the blocking antibody. Gupta-Bansal et al. teach that while factor B is a potential target for inhibiting activation of the alternative pathway, it is too unpredictable and unreliable to do inhibit factor B. Accordingly, one of ordinary skill the art would not select an ant-factor B antibody for inhibiting complement activation let alone an anti-factor B antibody that has a greater effectiveness at preventing factor B binding to properdin-bound C3b than preventing factor B binding to free C3b.

Owens et al. do not teach the aforementioned deficiencies of Gupta-Bansal et al.

Accordingly, Gupta-Bansal et al. in view of Owens et al. do not teach all of the limitations of independent claims 25, 33, and 40 and withdrawal of the obviousness rejection of claims 25, 33, and 40 is respectfully requested. Claims 26-32, 34-39, and 41-44 depend either directly or indirectly from claims 25, 33, 40, and are thus allowable because of the aforementioned arguments with respect to claims 25, 33, and 40. Withdrawal of this rejection is respectfully requested.

3. Claims 25-37 and 39-44 are rejected on the ground of nonstatutory obviousness-type double patenting

Claims 25-37 and 39-45 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,333,034 B1 ('034) in view of the Specification and Owens et al. (*Journal of Immunological Methods*, 1994, 168:149-165).

As discussed above, Gupta-Bansal et al. do not teach or suggest developing an anti-factor B antibody that in an *in vitro* assay has a greater effectiveness at

preventing factor B binding to properdin-bound C3b than preventing factor B binding to free C3b. Owens et al. do not teach aforementioned deficiencies of Gupta-Bansal et al. Accordingly, claims 1-7 of Gupta-Bansal et al. in view of Owens et al. do not teach all of the limitations of independent claims 25, 33, and 40 and withdrawal of the obviousness rejection of claims 25, 33, and 40 is respectfully requested. Claims 26-32, 34-39, and 41-44 depend either directly or indirectly from claims 25, 33, 40, and are thus allowable because of the aforementioned arguments with respect to claims 25, 33, and 40.

In view of the foregoing, it is respectfully submitted that the above-identified application is in condition for allowance, and allowance of the above-identified application is respectfully requested.

Please charge any deficiency or credit any overpayment in the fees for this amendment to our Deposit Account No. 20-0090.

Respectfully submitted,

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